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Follow-up study of Greek patients with West Nile virus neuroinvasive disease

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SUMMARY

Objectives: To investigate the extent to which Greek patients with West Nile virus neuroinvasive disease (WNND) recovered from the initial infection in 2010, when a West Nile virus (WNV) lineage 2 outbreak took place.
Methods: Twenty-two patients with WNND were examined 16 months after the onset of symptoms. The physical and mental function of the 22 survivors was evaluated.
Results: A considerable persistent morbidity and long length of time to recovery was observed. The most common symptoms were anorexia (77.3%) and muscle weakness (72.7%), followed by memory impairment (36.4%) and depression (22.7%). Older age was correlated with memory impairment, muscle weakness, and permanent damage. A complete recovery was seen in 7/22 (31.8%) patients, while three patients presented permanent damage. The critical time-point was 1 year after the onset of symptoms; at that time the patient's health status was either highly improved or had deteriorated irreversibly.
Conclusions: WNND is associated with considerable short- and long-term morbidity and mortality. Lineage 2 strains need further scientific attention. Public health measures are needed to prevent the infection, especially in the elderly with underlying diseases.

1. Introduction

West Nile virus (WNV) is a mosquito-borne flavivirus that was initially restricted to Africa, but sporadic cases and outbreaks now occur almost worldwide. Although the vast majority of WNV infections are asymptomatic or mild, approximately 1% of cases are characterized by virus entry into the central nervous system and infection of neural cells, resulting in neuroinvasive disease (WNND), which presents mainly as encephalitis, meningitis, meningoencephalitis, or acute flaccid paralysis.[1] Older age and immunosuppression are highly correlated with WNV neuroinvasiveness.

A large outbreak of WNV infections occurred in 2010 in Greece, a country from which the disease has not previously been reported.[2] Apart from the subclinical and mild cases, 197 patients presented with WNND, and 33 of them (17%) died. Cases were observed mainly in Central Macedonia, Northern Greece, where the incidence of WNND was 15 per 100 000 population, with the highest incidences in the districts of Pella and Imathia (28.26 and 27.06 per 100 000 population, respectively).[3] A few days after the outbreak started, WNV lineage 2 (strain Nea Santa/2010/Greece) was detected in mosquitoes collected in regions where human cases had been observed.[4] Identical strains were detected during all subsequent studies on blood donors, mosquitoes, wild birds, and sentinel chickens.[5–7] It was concluded that the outbreak was caused by this specific strain, which is genetically similar to that isolated in a dead goshawk in Hungary in 2004, presenting 44 mutations, one of them resulting in the amino acid substitution H249P in the NS3 protein.[8] This specific mutation has previously been associated with increased replication capacity in corvids in WNV lineage 1 strains.[9] Although many factors are implicated in the pathogenesis of WNV, this specific mutation might explain the difference in incidence and fatality rates between Greece and Hungary, where a yearly average of 6 WNND cases were diagnosed between 2003 and 2007, and 14 cases in 2008.[10]

Although a full recovery is seen in most patients with meningitis, the prognosis is much worse in encephalitis and flaccid paralysis cases, which are characterized by high fatality rates. Significant long-term morbidity is seen among survivors who experience neurological deficits, lasting from months to years after infection, including fatigue, muscle weakness, headache, persistent movement disorders, memory loss, and depression.[11–17] Most, if not all, post WNND studies have been conducted in areas where WNV lineage 1 strains have been detected (e.g., North America, Israel). The aim of the present study was to investigate and describe the extent to which patients with neurologic manifestations recover from their initial infection in Greece, where all sequences obtained during 2010–2011 belonged to lineage 2.

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2. Patients and methods

The present prospective study was performed in Giannitsa Hospital in the prefecture of Pella, where the highest incidence of WNND was observed in 2010 (28.26 per 100 000 population).[3] During August through September 2010, 31 patients with WNND were hospitalized. The laboratory diagnosis was made by detection of WNV IgM and IgG antibodies using an ELISA (WNV IgM capture DxSelect and WNV IgG DxSelect, respectively; Focus Diagnostics Inc., Cypress, CA, USA). Eight (25.8%) patients died while in hospital; by 1 year, an additional patient had died. The 22 survivors (11 male and 11 female) were asked to attend for an evaluation of their physical and mental function; all agreed to be tested (response rate 100%), and oral consent was obtained. The interview and re-evaluation were performed by one physician (AA) at 16 (± 1) months after symptom onset. Recovery was defined as a complete return to baseline function, i.e. that prior to infection. A statistical analysis was performed using binary logistic regression with the IBM SPSS 19 package. Odds ratios (OR) and 95% confidence intervals (95% CIs) were obtained and statistical significance was defined as a two-tailed p-value of less than 0.05.

3. Results and discussion

Twenty-two WNND patients (11 male and 11 female) were followed-up at 16 (± 1) months after symptom onset. Most of them ($n = 20$) were patients with encephalitis; two (one male and one female) had meningoencephalitis (cases 3 and 19 in Table 1). The median age of the patients was 70 years (range 23–87 years), with males being significantly younger than females ($p < 0.05$) (Table 1). Most patients (17/22, 77.3%) had an underlying disease: 15 had hypertension and five had diabetes mellitus. The mean hospitalization time was 8.09 days (range 5–21 days) and differed significantly between male and female patients. Persistence of WNV IgM antibodies was observed in one male patient at 220 days after the onset of symptoms;[18] these were not detectable at the 18-month follow-up.

A brief description of the main symptoms, underlying diseases and sequelae in each of the 22 cases is given in Table 2. The most common persisting symptoms were anorexia (77.3%), leading to weight loss (up to 30 kg), and muscle weakness (72.7%), followed by memory impairment (36.4%) and depression (22.7%) (Table 1). Patients with depression were evaluated and followed-up by a psychiatrist. A complete recovery was seen in 7/22 (31.8%) patients and improvement in 12 patients, while three presented permanent impairments. Although improvement was usually observed at 1–2 months after the onset of symptoms, the critical time-point for the health status of the patient was at 1 year, when the patient's condition was either highly improved or had deteriorated irreversibly. One female patient (case 10) who had an underlying disease was hospitalized six times during the 16-month period (once in the intensive care unit), because of respiratory or urinary infections. An additional female patient (case 3) visited the hospital several times because of severe constipation (gut paralysis); the symptom lasted for approximately 1.5 year, and then the patient started to gain the lost weight (30 kg).

Male patients recovered earlier than females ($p < 0.05$), most probably due to their younger age and the absence of predisposing conditions in most of the male patients. Increased age was correlated with the presence of underlying disease, memory impairment, anorexia, sweating, muscle weakness, tremor, and permanent damage ($p < 0.05$); in contrast, depression, dizziness, and hearing loss were not age-dependent. The mean time needed for complete recovery in the seven patients was 6.26 months, with a trend of earlier recovery for the male patients (4.3 months vs. 8.4 months in females). With regard to the three patients who presented permanent impairment (bedridden, dementia), they were all older than 70 years (74, 86, and 87 years). Interestingly, an 83-year-old female patient with underlying syndromes and severe muscle weakness, started to recover 10 months after the onset of disease, and her status was premorbid at the 16-month follow-up.

WNV encephalitis is associated with considerable short-term and long-term morbidity and mortality.[19] The in-hospital fatality rate of patients with WNND of the present study was 25.8%, which is among the highest reported so far.[15,20–22] The delayed clearance of the virus correlates with frequent neurological sequelae. The findings at the 16-month follow-up demonstrated a spectrum of functional and strength outcomes, with a considerable persistent morbidity, since more than half of the survivors had not returned to their previous functional level. This is consistent with studies from North America, where the responsible WNV strain belonged to lineage 1.[15]

Anorexia and muscle weakness were the most common persistent symptoms. Similarly, symptom duration of more than 3 months was observed for 48.7% of WNV encephalitis patients in Denver, Colorado; muscle weakness, muscle pain, and headache were the most frequently reported persistent symptoms.[23] Two of our patients required supplemental oxygen for 6 months. Neuromuscular respiratory failure is the most severe manifestation of WNV poliomyelitis, and although successful extubation and recovery can occur, respiratory involvement is associated with a high fatality rate (>50%).[19]

Preexisting comorbid conditions play a significant role in a longer recovery.[24] This was observed in the present study: five of the seven recovered patients were relatively young (25–55

Table 1
Demographic and clinical characteristics of study patients with West Nile virus neuroinvasive disease

Variable	Males ($n = 11$)	Females ($n = 11$)	Total ($n = 22$)	p-Value	OR	95% CI
Age, years, median (range)	42 (23–86)	71 (63–87)	70 (23–87)	0.03	1.08	1.0–1.1
Underlying disease (%)	6 (54.5)	11 (100)	17 (77.3)	0.99	1.34	0
Days in hospital, mean (range, SD)	6.27 (5–9, 1.34)	9.91 (5–21, 4.67)	8.09 (5–21, 3.84)	0.04	1.77	1.0–3.0
Anorexia (%)	7 (63.6)	10 (90.9)	17 (77.3)	0.15	5.71	0.5–62.6
Tremor (%)	4 (36.4)	0 (0)	4 (18.2)	0.99	9.23[a]	
Muscle weakness (%)	6 (54.5)	10 (90.9)	16 (72.7)	0.08	8.33	0.7–89.4
Dizziness (%)	1 (9.1)	3 (27.3)	4 (18.2)	0.29	3.75	0.3–43.3
Intense sweating (%)	0 (0)	2 (18.2)	2 (9.1)	0.15	5.71	0.5–62.6
Depression (%)	1 (9.1)	4 (36.4)	5 (22.7)	0,15	5.71	0.5–62.6
Memory problems (%)	4 (36.4)	4 (36.4)	8 (36.4)	1.0	1.00	0.1–5.6
Hearing loss (%)	2 (18.2)	1 (9.1)	3 (13.6)	0.54	0.45	0.03–5.8
Permanent damage (%)	1 (9.1)	2 (18.2)	3 (13.6)	0.54	2.22	0.1–28.8
Complete recovery (%)	6 (54.5)	1 (9.1)	7 (31.8)	0.04	12.00[a]	1.1–128.8
Months to recovery, mean (range) ($n = 7$)	4.3 (1–12)	8.4 (1–12)	6.26 (1–12)	0.31	1.48	0.6–3.2

OR, odds ratio (females:males); CI, confidence interval; SD, standard deviation.
[a] OR males:females.

Table 2
Main characteristics of the patients included in the study

Case No.	Gender	Age	Co-morbidities	Time in hospital	Main symptoms during convalescence	Time to recovery; sequelae
1	Female	65	Hypertension	9 days	Weight loss (~10 kg), respiratory failure (supplemental oxygen for 6 months), permanent phrenic nerve palsy, major depression	Not fully recovered; elevation of left hemidiaphragm, major depression
2	Female	79	Hypertension	10 days	Anorexia for 3 months, muscle weakness, dizziness, intense sweating, impaired memory	Not fully recovered; muscle weakness, persistent dizziness, impaired memory
3	Female	70	Hypertension	11 days	Anorexia for 1 year, weight loss (>30 kg), bedridden for 8–10 months, Guillain–Barré–like quadriplegia for 1 year, muscle weakness, emotional instability, major depression, abdominal pain, severe constipation for 1.5 years	Not fully recovered; pulmonary hypertension, muscle weakness, major depression
4	Female	63	Hypertension, type II diabetes	8 days	Muscle weakness, anorexia, sweating, unregulated diabetes for 8 months, depression	Not fully recovered; muscle weakness, major depression
5	Female	74	Hypertension	10 days	Weight loss, severe anorexia for 6 months, amnesia, lack of concentration, muscle weakness of lower limbs, bedridden	Permanent impairment; dementia, bedridden
6	Female	83	Hypertension, heart failure	6 days	Respiratory insufficiency – supplemental oxygen (at home) for 6 months, anorexia for 3 months, weight loss (10 kg), muscular weakness for 6 months, unable to walk (used walker for 3 months), bad mood	10 months
7	Female	71	Parkinson's disease	5 days	Muscle weakness, use of wheelchair, anorexia, weight loss (10 kg), constipation, insomnia, bad mood for 1 year	Not fully recovered; muscle weakness
8	Female	87	Hypertension	15 days	Weight loss, weakness, unable to walk (initially required a walker, then bedridden), impaired memory	Permanent impairment; bedridden, dementia
9	Female	70	Hypertension thyroidectomy	9 days	Weight loss (>10 kg), muscle weakness, headache, fatigue, dizziness, bad mood, depression, unable to walk for 1 month (walker required)	Not fully recovered; headache, dizziness, major depression
10	Female	72	Hypertension, breast cancer	21 days	Headache, memory impairment, hearing loss, muscle weakness, numbness in the upper extremities, bedridden for 2 months	Not fully recovered; gait instability, headache, memory impairment
11	Female	70	Hypertension	5 days	Bad mood for a short time, dizziness	Not fully recovered; dizziness
12	Male	55	Hypertension, abdominal aortic aneurysm	5 days	Tremor in the upper extremities for 6 months	6 months
13	Male	34	No	5 days	Anorexia and muscle weakness for 1 month, tremor in upper extremities, bad mood for 5 months	5 months
14	Male	30	No	6 days	Tremor of the upper extremities, emotional instability, bad mood	1 year
15	Male	42	No	7 days	Anorexia for 2 months, weight loss, muscle weakness for 1 month, tremor in upper extremities, bad mood	Not fully recovered; tremor
16	Male	25	No	5 days	Headache	1 month
17	Male	23	No	6 days	Headache	1 month
18	Male	70	Hypertension	9 days	Weight loss, muscle weakness for 4–5 months, hearing loss, memory impairment	Not fully recovered; hearing loss, memory impairment
19	Male	86	Hypertension, diabetes, chronic renal failure	7 days	Severe muscle weakness, atrophy, amnesia	Permanent impairment; bedridden, dementia
20	Male	76	Hypertension, diabetes, dyslipidemia	8 days	Muscle weakness, anorexia for 1 month, weight loss, behavior disorder, memory impairment, bad mood, depression	Not fully recovered; major depression, amnesia
21	Male	42	Hypertension, diabetes, coronary disease	5 days	Weight loss (8–10 kg), dizziness, bad mood for 1 month, muscle weakness for 1 month	2 months
22	Male	80	Diabetes	6 days	Weight loss, memory impairment, hearing loss	Not fully recovered; memory impairment, hearing loss

years old) without preexisting medical conditions; however, an 83-year-old female patient with underlying disease recovered completely in 10 months. Long-term residual effects are also seen in non-neuroinvasive cases.[14,25] Further studies are needed to elucidate the factors that play a role in the severity of the disease and the time to recovery.

Limitations of the present study were the small sample size and the selection bias due to sampling of the patients from only one

hospital. However, it was evident that during the outbreak in Greece the findings in WNND patients were similar to those seen in North America, suggesting that the pathogenicity to humans is strain-related rather than lineage-related.

Since its emergence in Greece in 2010, WNV lineage 2 has resulted in more than 250 neuroinvasive cases with increased morbidity and mortality, and many of the patients are still suffering from clinical and functional disabilities. Although the epidemiology of WNV is unpredicted, the increasing spread of lineage 2 strains might be of public health concern, and needs further scientific attention. Public health measures are needed to prevent the infection, especially in the elderly with underlying diseases.

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